REMARKS

I. FORMAL MATTERS:

Claims 1, 7-8, 13-16, 25, 28-34, 39-40, 47-48, 55-56 and 59-68 are pending after entry of the amendments set forth herein.

Claims 62-68 are new.

Claim 1 and 25 are currently amended. Support for these amendments is found in the specification, for example, at page 11, paragraph [0042]. Applicants note that, in accordance with MPEP § 2173.05(i), if alternative elements are positively recited in the specification, they may be explicitly excluded in the claims (see, e.g., *In re Johnson,* 558 F.2d 1008).

The Applicants have added new claims 63-68. Support for these amendments is found in the specification, for example, at page 11, paragraph [0042] and page 14, paragraph [0055].

The Applicants assert that these amendments add no new matter and their entry is respectfully requested.

II. Interview Summary

The Applicants conducted an interview on July 25, 2008.

- Names of participants: Examiner Robert Crow, Carol L. Francis and David A. Carpenter.
- Exhibits or demonstrations: none
- Claims discussed: Claim 1.
- Specific prior art discussed: Lizardi et al., US 5,312,728.
- Examiner Crow provided guidance as to the types of probe structures and amendments that may overcome the rejection under 35 U.S.C. §103(a). Accordingly, the Applicants have filed the following remarks and amendments.

III. REJECTIONS UNDER §103(A)

Claims 1, 7-8, 12, 14-16, 25, and 28-34 are rejected under 35 U.S.C. §103(a) as being unpatentable over Blackburn et al., (U.S. 6,264,825; henceforth "Blackburn") in view of Lizardi et al., (U.S. Patent 5,312,728: henceforth "Lizardi").

In order to establish a *prima-facie* case for obviousness under 35 U.S.C. §103 the Examiner is required to show, *inter alia*, that the prior art references taken together as a whole teach or suggest all

claim limitations of the rejected claims.[1] This includes portions of the cited art that would lead away from the claimed invention.[2] Notably, the combination of the references as a whole is still pertinent law under the determination of non-obviousness under *KSR Int'l Co. v. Teleflex Inc.*[3]

The Examiner has proposed a combination of Blackburn with Lizardi. The Applicants respectfully traverse and assert that the proposed combination taken as a whole does not teach or suggest all limitations of the currently amended claims.

Blackburn is cited for its asserted disclosure of an oligonucleotide probe immobilized on an electrode, wherein the probe comprises a redox moiety and a probe nucleotide sequence which hybridizes with a target nucleotide sequence. However, as discussed during the interview, Blackburn fails to provide for the structural elements that provide for the first and second positions as set out in the claims.

The Examiner asserted Lizardi provides disclosure of a molecular "switch" in the probe structure. As discussed during the interview, it is this disclosure upon which the Examiner has relied to provide the structure element of the claimed invention, namely that

- in the absence of hybridization between the target and the probe, the redox moiety is located in a first position relative to the electrode and,
- in the presence of hybridization between the target and the probe, said redox moiety being located in a second position relative to the electrode,
- said first and second positions giving rise to distinguishable redox events detectable by the electrode wherein, relative to the first position, the second position promotes electron transduction between the redox moiety and the electrode,
- wherein the second position results from a disruption of internal hybridization in the probe as the result of the specific interaction between a region in the probe and the target, and
- wherein the second position is closer to the electrode than the first position

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[1] MPEP § 2141.02(II) Distilling an invention down to the "gist" or "thrust" of an invention disregards the requirement of analyzing the subject matter "as a whole." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). See also *Jones v. Hardy*, 727 F.2d 1524, 1530, 220 USPQ 1021, 1026 (Fed. Cir. 1984) ("treating the advantage as the invention disregards statutory requirement that the invention be viewed 'as a whole'"); *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1 USPQ2d 1593 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987) (district court improperly distilled claims down to a one word solution to a problem).

[2] MPEP §2141.02(VI) A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)

[3] *KSR Int'l Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1395 (US 2007) as discussed within the context of Examiners applying the *Graham* factors as they relate to the *KSR* holding in the Federal Register: "Ascertaining the differences between

However, Lizardi fails to teach or suggest oligonucleotide probes other than RNA probes having as per the amended claims that have the required structural feature. Specifically, the Examiner relies on Example V of Lizardi, where the recited probe structure requires 5 distinct elements: 1) a probe sequence 2) a first switch sequence 3) a second switch sequence 4) a spacer element and 5) a replicatable ***RNA*** moiety. (Lizardi column 14, lines 5-18). The replicatable RNA moiety is required because the method of detecting whether a probe has interacted with the target sequence is by amplification of the replicatable RNA moiety by the RNA-directed- RNA polymerase, Q-beta replicase (Lizardi, column 3, lines 3-8 and column 8 lines 35-40). There can be no detection of the probe/target interaction without the replicatable RNA moiety, as this is the part of the probe that the Q-beta replicase will act upon. Indeed, when referring to these probes, Lizardi states: "They ***all*** utilize the exponential replication of a replicatable RNA by an RNA-directed RNA polymerase to generate a readily detectible signal" (Lizardi column 8, lines 27-30. Emphasis added).

Furthermore, Example V requires that upon binding of the probe to the target sequence the probe is designed to undergo an internal conformational change, resulting in the formation of a ribozyme. (Lizardi column 14, lines 24-33 and Figures 12 and 13). Ribozymes are RNA-based structures only, and cannot be formed by DNA.

Because Lizardi teaches only RNA based probes having a "switch" feature, and the claims as currently amended exclude RNA oligonucleotides, Lizardi fails to teach or suggest all elements of the claims. Indeed, when describing the only other probes disclosed in Lizardi -- DNA probes -- Lizardi fails to include a "switch" element. Indeed, the only DNA probe disclosed by Lizardi is illustrated in Figs. 1-3. Lizardi indicates that, in the absence of target hybridization (Fig. 1), the DNA probe has a hairpin positioned centrally within the probe such that the 5' and 3' ends are of equal length. In the presence of target (element 8 of Figs. 2 and 3), Lizardi's DNA probe is opened such that the 5' and 3' ends are or equal length. Thus, there is no teaching of a DNA probe that, if modified by the teaching of Blackburn as set out in the rejection, would provide for, in the absence of target hybridization, a "first position" of a redox moiety that is further from an electrode on which the DNA probe may be immobilized and a "second position" in the presence of hybridized target so that the redox moiety would be closer to the electrode. Indeed, if, for example, Lizardi's DNA probes were immobilized on an electrode and the opposite end were attached to a redox moiety, the redox moiety would be *closer* to the electrode in the absence of hybridized target. *This is the opposite of the claimed invention.*

Given the direction in Lizardi that a "switch" element is included only for the purposes of providing a replicatable RNA moiety and/or for formation of a ribozyme – *both of which are necessarily*

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the claimed invention and the prior art requires interpreting the claim language, and considering both the invention and the

limited to RNA molecules -- one of ordinary skill in the art would *not* be motivated to modify the DNA probe to include such a "switch" structure. Thus, when read as a whole, Lizardi provides no teaching or suggestion to provide DNA probes having a "switch" element.

As such, the Applicants respectfully request withdrawal of the rejection of claims 1, 7-8, 12, 14-16, 25, and 28-34 under 35 U.S.C. §103(a).

Claim 13 is rejected under 35 U.S.C. §103(a) as being unpatentable over Blackburn in view of Lizardi and further in view of Rothberg et al., (U.S. Published Application 2002/0012930; henceforth "Rothberg").

As demonstrated above, the combination of Blackburn and Lizardi does not create a prima facie case of obviousness, because the proposed combination does not teach or suggest all elements of the claims.

As Rothberg was cited solely for the loop element of Claim 13, Rothberg fails to cure the fundamental deficiency in the combined disclosures of Blackburn and Lizardi.

Accordingly, the combined teaching of Blackburn in view of Lizardi, in further view of Rothberg fails to teach or suggest all elements of the claimed invention. Therefore, Claim 13 is not obvious under 35 U.S.C. §103(a) over Blackburn in view of Lizardi in further view of Rothberg and this rejection may be withdrawn.

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prior art as a whole." Federal Register / Vol. 72, No. 195 / Wednesday, October 10, 2007 / Notices, page 57528.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCSB-510CIP.

Respectfully submitted,
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Date: July 29, 2008

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